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(54) Title: COMBINATION DRUG THERAPY

(57) Abstract: The invention provides antineoplastic composition containing an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase type I enzyme activity.

COMBINATION DRUG THERAPY

BACKGROUND OF THE INVENTION

This invention relates to cancer chemotherapy.

Chemotherapy for cancer is used primarily for the treatment of nonoperable or metastatic tumors or to supplement primary surgical therapy. Traditional chemotherapeutic approaches to cancer treatment involve administering agents which are cytotoxic to tumor cells. However, often such agents also affect normal cells resulting in adverse side effects.

SUMMARY OF THE INVENTION

The invention features a combination of therapeutic agents which significantly inhibits tumor cell growth with low toxicity. Tumor growth and development in mammals is reduced following administration of a combination of a topoisomerase I inhibitor and an inhibitor of angiogenesis. Accordingly, the invention provides an antineoplastic formulation containing a camptothecin compound and a thrombospondin compound. The camptothecin compound is camptothecin or an analogue thereof, e.g., irinotecan (camptosar, CPT-11, 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonloxycamptothecin), topotecan, 20-S-camptothecin (20(S)CPT), 10,11-methylenedioxy-CPT (10,11-CPT), 7-ethyl-10-hydroxy-CPT (SN38), 9-AC^3 (NSC603071), TTN (NSC 609699), or 9-dimethylaminomethyl-10-hydroxycamptothecin. A thrombospondin compound is a polypeptide which contains at least one type I properdin repeat sequence and inhibits formation of blood vessels. For example, the thrombospondin compound is purified or recombinant thrombospondin-1(TSP1) or thrombospondin-2 (TSP2) or a biologically active fragment thereof. Preferably, a biologically active fragment contains the amino acid sequence XXXWXXWXXWXXCXXXXXXXXXXXXXXXCXXXXXXXXXXXXXXXXXX XXXXXXCXXXXC (SEQ ID NO:1), WSPS (SEQ ID NO:2), KRFK (SEQ ID NO:3), or CSVTCG (SEQ ID NO:4). For example, a fragment of TSP1 contains

the amino acid sequence DGGWSHWSPWSSCSVTCGDGVITRIRLCNSPSPQMNGKPCEGEARETKAC KKDACPI (SEQ ID NO:5), and a fragment of TSP2 contains the amino acid sequence of DGGWSHWSPWSSCSVTCGVGNITRIRLCNSPVPQMGGKNCKGSGRETKA CQGAPCPI (SEQ ID NO:6).

Also within the invention is method of inhibiting tumor cell growth in a mammal by administering to the mammal a composition containing an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity. The angiogenesis inhibitor is administered before the topoisomerase inhibitor; alternatively the topoisomerase I inhibitor is administered before the angiogenesis inhibitor. In some cases, the inhibitors are administered simultaneously. For example, the method includes the steps of administering to the mammal a camptothecin compound and a thrombospondin compound. Preferably, the mammal is a human; however, the methods are applicable for veterinary use. For example, the agents are administered to treat tumors in cats, dogs, cows, pigs, and the like. The compounds are administered together in a mixture, simultaneously via the same or different route, or sequentially via the same or different route. The compositions are delivered systemically or locally, i.e., directly or in close proximity to a tumor mass.

The combination drug formulation and methods of the invention are safer and more effective than conventional chemotherapeutic approaches, including known combination approaches. The combination of a camptothecin compound and a thrombospondin compound inhibited tumor growth in the absence of significant toxicity.

Other features, objects, and advantages of the invention will be apparent from the description and and from the claims.

DETAILED DESCRIPTION

Angiogenesis inhibitors and inhibitors of topoisomerase I such as camptothecin compounds are used to treat tumors in mammals; however, each of these agents alone is not effective in the treatment of human cancers. The

combined therapeutic regimen results in a synergistic inhibition of tumor cell growth. As is described below, a combination of these agents confers greater neoplastic activity than either of these classes of agents alone.

Inhibition of DNA topoisomerase I enzymes

DNA topoisomerase type 1 enzymes function to effect the levels of DNA supercoiling. A biological activity of topoisomerase I is reduction in the level of DNA supercoiling. DNA transformations performed by DNA topoisomerases are accomplished by the cleavage of either a single strand or both strands the nucleic acid. Type 1 topoisomerases can relax supercoiled DNA (except of reverse gyrases), catenate (or decatenate) single-stranded circular DNAs or duplexes providing that at least one of the molecules contains a nick or gap, or interact with single-stranded circles to introduce topological knots.

Enzyme inhibition leads to the stabilization of the covalent-enzyme-DNA complex (cleavable complex). Topoisomerase type I inhibitory activity of camptothecin or derivatives thereof is determined using methods known in the art, e.g., by the cleavable complex *in vitro* assay described in Hsiang, Y. et al., 1985, J. Biol. Chem., 260:14873-14878. An increase in the amount of compound in the presence of a compound compared to the amount in the absence of the compound indicates that the compound has topoisomerase I inhibitory activity. Activity measured by this or similar assays correlates well with *in vivo* anti-tumor activity of topoisomerase inhibitors in animal models of cancer, e.g., camptothecin and its analogs (Hsiang et al., 1989, Cancer Research, 49:4385-4389 (1989) and Jaxel et al., Cancer Research, 49:1465-1469).

Camptothecin compounds

Camptothecin is a naturally-occurring compound derived from the Oriental tree Camptotheca acuminata. Although it has been shown to have cytotoxic effects, its use clinically is limited due to unpredictable and formidable toxicities. Two water-soluble camptothecin analogs, topotecan and CPT-11, are safer and better tolerated. Additional water soluble camptothecins are known in the art, e.g., described in U.S. Patent No. 6, 100,273. Other camptothecin derivatives include 20-S-camptothecin (20(S)CPT), 10,11-methylenedioxy-CPT (10,11-CPT) and 7-ethyl-10-hydroxy-CPT (SN38). Camptothecin and its derivatives are inhibitors of

DNA topoisomerase and stimulate DNA cleavage. Other topoisomerase I inhibitors include DNA minor groove binders such as Hoechst 33258 and DNA intercalators such as benzophenanthridine alkaloids and indolocarbazole derivatives, as well as drugs which prevent or reverse topoisomerase I-DNA complex formation (e.g., beta-lapachone, diospyrin, topostatin, topostin, flavonoids).

Inhibition of Angiogenesis

Angiogenesis is a process of tissue vascularization that involves the growth of new developing blood vessels into a tissue. This process is also referred to as neovascularization and is mediated by infiltration of endothelial cells and smooth muscle cells. Blood vessels can sprout from pre-existing vessels, de-novo development of vessels can arise from precursor cells (vasculogenesis), or existing small vessels can enlarge in diameter.

Inhibiting angiogenesis at or near a tumor site can restrict tumor growth. Inhibit ors of angiogenesis include endothelial cell response inhibitors, including collagenase inhibitors, basement membrane turnover inhibitors, angiostatic steroids, fungal-derived angiogenesis inhibitors, platelet factor 4, thrombospondin, arthritis drugs such as D-penicillamine and gold thiomalate, vitamin D analogs, and alpha-interferon.

Angiogenesis or inhibition thereof is determined by measuring the formation of "microvessels" *in vitro* in collagen gel cultures or *in vivo.* A reduction in the amount of new blood vessel formation in the presence of a compound compared to the level in the absence of the compound indicates that the compound is an inhibitor of angiogenesis. A reduction in the amount of expression of angiogenic factors, e.g., vascular endothelial growth factor (VEGF) or VEGF receptors also indicates that a compound inhibits angiogenesis.

Thrombospondin Compounds

Thrombospondins are polypeptide compounds which are characterized by a type I (properdin) repeat, e.g., SEQ ID NO:1, 5 or 6. Thrombospondin-1 is a 450 kDa extracellular matrix protein that functions to suppresses capillary growth. The antiangiogenic region of TSP1 maps to the type I (properdin) repeats. Naturally-

occurring TSP1 is a trimeric extracellular matrix protein that is held together by two cysteine residues. It is one of a family of five TSP proteins that have been described to date. With the exception of TSP5, members of the thrombospondin family are also characterized as having heparin binding capability. However, a heparin binding domain (e.g., located in the amino terminal portion of a naturally-occurring thrombospondin monomer) need not be present for antiangiogenic activity.

Biologically active fragments, mutants, or analogues of TSP1 or TSP are tested for the ability to inhibit angiogenesis. Fragments are recombinantly produced or generated by enzymatic digestion. Fragments and analogues of human thrombospondin with antiangiogensis activity are known in the art (e.g., as described in U.S. Patent No. 5,192,744 or U.S. Patent No. 5,840,692). Inhibition of angiogenesis is measured using methods well known in the art, e.g., a standard in vivo corneal neovascularization assay (Polverini et al., 1991, Methods. Enzymol. 198:440-450).

Therapeutic Administration

Camptothecin or thrombospodin compounds are formulated as colloidal dispersions or dissolved in a pharmaceutically-acceptable diluent, e.g., sterile water, physiological saline, or a dextrose solution (e.g., 20% dextrose). Alternatively, a camptothecin compound is administered as a liposomal composition; methods for preparing multilamellar liposome-incorporated camptothecin (LCPT) are known in the art (e.g., as described by Clements et al., 1996, Anticancer Drugs 7:851).

The combination drug therapy is used to treat solid, non-solid, and multiple-drug resistant tumors. The tumor is a carcinoma or sarcoma. Tumors to be treated include leukemia, lymphoma, as well as cancers of the colon, lung, melanoma, ovarian, breast, prostate cancer, pancreatic, CNS, liver, and urinary bladder.

An effective amount of a compound is preferably from about 0.1 mg/kg to about 150 mg/kg. The compounds are administered using methods known in the art. They are administered locally, e.g., at the site of a solid tumor, or systemically, e.g., in the case of diffuse, or disseminated tumors. To treat

accessible solid tumors, either agent or both agents are administered in a slow release implant or pellets surgically introduced into or near the site of a solid tumor. Preferably, the compound is administered orally, topically or parenterally, e.g., subcutaneously, intraperitoneally, intramuscularly, and intravenously. The compounds are administered as an admixture, or in separate formulations either simultaneously, or sequentially.

Thrombospondin-1 and Irinotecan Inhibit Tumor Growth

The antineoplastic activity of TSP plus CPT-11 was evaluated in an art – recognized model for cancer, nude mice bearing xenografts of the human colon tumor cell line HT29. TSP and CPT-11 did not interact *in vitro* to produce enhanced tumor cell cytotoxicity. However, *in vivo*, a synergistic antineoplastic effect was observed after administration of TSP and CPT-11 in combination.

For *in vivo* studies, nude mice were inoculated subcutaneously in the left axillary region with 5×10^6 HT29 cells. When tumors were palpable (approximately 50 mg), mice were divided into groups (n=15-22) and treated as follows: (i) no treatment; (ii) TSP alone (5-40 mg/kg intraperitoneally) (iii) CPT-11 alone (100-300 mg/kg intraperitoneally); or (iv) TSP (20 mg/kg) + CPT-11 (150 mg/kg). TSP was injected daily while CPT-11 was administered on days 0, 7, 14, and 21. Mice were weighed and tumors measured twice weekly. By day 28, TSP alone (10 or 20 mg/kg) significantly ($p<0.05$) inhibited tumor growth. Treated tumor size/Control tumor size (T/C) equaled 0.64 or 0.57, respectively. Treatment with other doses of TSP was less effective. CPT-11 alone, at all doses, also significantly ($p<0.001$) inhibited tumor growth with and average T/C of 0.3. However, CPT-11 at 250 mg/kg and 300 mg/kg induced significant toxicity and mortality. When TSP was combined with CPT-11, a highly significant inhibition of tumor growth was observed compared to control (T/C = 0.1, with p=0.00002) and compared to CPT-11 alone (p=0.0008). The inhibition of tumor growth observed with the combination drug therapy was without significant toxicity. These results indicate that combinations of chemotherapeutic agents (e.g., topoisomerase I inhibitors such as camptothecins) and agents which inhibit angiogenesis (e.g., thrombospondins) are useful to inhibit tumor growth while avoiding detrimental side effects such as toxicity.

Other embodiments are within the following claims.

What is claimed is:

1. An antineoplastic composition comprising an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity.

2. The antineoplastic composition of claim 1, wherein said inhibitor of angiogenesis is a thrombospondin compound.

3. The antineoplastic composition of claim 1, wherein said inhibitor of DNA topoisomerase I enzyme activity is a camptothecin compound.

4. The antineoplastic composition of claim 2, wherein said thrombospondin compound is thrombospondin-1.

5. The antineoplastic composition of claim 2, wherein said thrombospondin compound is thrombospondin-2.

6. The antineoplastic composition of claim 3, wherein said camptothecin compound is irinotecan (CPT-11).

7. The antineoplastic composition of claim 3, wherein said camptothecin compound is topotecan.

8. The antineoplastic composition of claim 3, wherein said camptothecin compound is selected from the group consisting of 20-S-camptothecin (20(S)CPT), 10,11-methylenedioxy-CPT (10,11-CPT), 7-ethyl-10-hydroxy-CPT (SN38), and 9-AC[3].

9. A method of inhibiting tumor cell growth in a mammal, comprising administering to said mammal a composition comprising an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase I enzyme activity.

10. The method of claim 9, wherein said inhibitor of angiogenesis is a thrombospondin compound.

11. The method of claim 9, wherein said inhibitor of DNA topoisomerase I enzyme activity is a camptothecin compound.

12. The method of claim 10, wherein said thrombospondin compound is thrombospondin-1.

13. The method of claim 10, wherein said thrombospondin compound is thrombospondin-2.

14. The method of claim 11, wherein said camptothecin compound is irinotecan (CPT-11).

15. The method of claim 11, wherein said camptothecin compound is topotecan.

16. The method of claim 11, wherein said camptothecin compound is selected from the group consisting of 20-S-camptothecin (20(S)CPT), 10,11-methylenedioxy-CPT (10,11-CPT), 7-ethyl-10-hydroxy-CPT (SN38), and 9-AC[3].

17. The method of claim 9, wherein said mammal is a human.

18. The method of claim 9, wherein said inhibitor of angiogenesis is administered prior to said inhibitor of DNA topoisomerase I enzyme activity.

19. The method of claim 9, wherein said inhibitor of DNA topoisomerase I enzyme activity is administered prior to said inhibitor of angiogenesis .

20. The method of claim 9, wherein said inhibitor of angiogenesis and said inhibitor of DNA topoisomerase I enzyme activity are administered simultaneously.

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(74) Agent: **BEATTIE, Ingrid, A.**; Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., One Financial Center, Boston, MA 02111 (US).

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(54) Title: ANTINEOPLASTIC COMBINATION COMPRISING AN INHIBITOR OF ANGIOGENESIS AND AN INHIBITOR OF DNA TOPOISOMERASE I ENZYME ACTIVITY

(57) Abstract: The invention provides antineoplastic composition containing an inhibitor of angiogenesis and an inhibitor of DNA topoisomerase type I enzyme activity.

INTERNATIONAL SEARCH REPORT

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; March 2000 (2000-03) ALLEGRINI GIAEOMO ET AL: "The angiogenesis inhibitor thrombospondin-1 plus irinotecan significantly inhibit tumor growth in human colon tumor bearing nude mice." Database accession no. PREV200000275647 XP002180182 abstract & PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, no. 41, March 2000 (2000-03), page 813 XP001019254 91st Annual Meeting of the American Association for Cancer Research.;San Francisco, California, USA; April 01-05, 2000, March, 2000 ISSN: 0197-016X -/--	1-20

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
	the whole document ---	
A	WO 93 09782 A (SMITHKLINE BEECHAM CORP) 27 May 1993 (1993-05-27) the whole document ---	1-20
A	WO 92 14470 A (SMITHKLINE BEECHAM CORP) 3 September 1992 (1992-09-03) the whole document ---	1-20
A	WO 91 10424 A (UNIV NORTHWESTERN) 25 July 1991 (1991-07-25) the whole document -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

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